pregnancy-induced hypertension or a history of decreased fetal movement supported by persistently poor fetal testing over one to two days. Pregnancy should rarely be carried beyond 40 weeks except in women well controlled by diet with no other risk factors. In such situations, fetal surveillance should be used until cervical ripening or 42 weeks of gestation. Elective interventions, such as a cesarean section at 38 weeks or inductions of labor, should be preceded by evidence of fetal lung maturity.

The long-term morbidity of gestational diabetes includes type II or non–insulin-dependent diabetes mellitus. This disorder in turn is associated with a higher frequency of end-organ failure, such as kidneys, eyes, and heart, especially in minority populations. Continued attention to diet, weight control, and exercise may reduce these risks.

At eight weeks postpartum, women with gestational diabetes mellitus should be tested with a standard 75-gram, two-hour glucose tolerance test. Women with abnormal test results should be seen by a diabetologist.

Although the risk of congenital anomalies is not reduced by diagnosing diabetes during pregnancy, this approach identifies a population that should undergo preconception counseling. Such counseling begins before the next pregnancy, which should be planned. It encourages women at risk for gestational diabetes to begin good glucose control two to three cycles before a planned pregnancy. This approach is associated with a substantial reduction in congenital anomalies.

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RU 486 (Mifepristone)

RECENTLY APPROVED for use as an abortifacient in the United Kingdom and in France, RU 486 (mifepristone) is the first of a new class of antiprogestins. When given in early pregnancy, it saturates progesterone receptors in the endometrium but does not act as an agonist. Progesterone is essential to sustain an early pregnancy, and if its action is blocked by RU 486, an abortion ensues. When given in a single oral dose of 600 mg before seven weeks' gestation, abortion rates of 80% to 90% can be achieved. If the dose of RU 486 is followed in 36 to 48 hours by a small dose of prostaglandin, the efficacy increases to more than 90%. The prostaglandin can be given as an intramuscular injection, a vaginal suppository, or orally by tablet. In the largest series of such abortions reported from France, the abortion rate was 96%. Morbidity rates have been low, although heavy bleeding can require curettage for management.

RU 486 may have a broad range of uses in reproductive medicine. When given to both pregnant and nonpregnant women, it causes softening and dilation of the cervix. When given 24 hours before beginning a second-trimester abortion by labor induction, it can reduce the time required by more than 50%. Its usefulness for inducing labor at term remains to be studied. Experience with RU 486 as medical therapy for ectopic pregnancy has not been encouraging. One small study found that daily treatment of endometriosis with RU 486 for three months led to a relief of symptoms without objective lessening in the extent of disease.

RU 486 may have applications beyond reproductive medicine. For example, the drug might be useful in treating women with metastatic breast cancer resistant to current therapies. In a study of 22 women after menopause or oophorectomy with therapy-resistant metastatic breast cancer, 18% showed a response to the drug at three months. When given in doses larger than that required to block progesterone receptors, RU 486 also blocks glucocorticoid receptors; the drug has been shown to be useful in treating Cushing's syndrome. Studies of its use in treating glaucoma and meningioma are in progress.

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Management of Hirsutism

HIRSUTISM, or male-pattern hair growth in women, is a common cosmetic complaint. The differential diagnosis includes pathophysiologic processes that either increase androgen production (polycystic ovary syndrome, late-onset congenital adrenal hyperplasia, Cushing's syndrome, or neoplasm) or increase androgen activity at the hair follicle itself (increased 5α-reductase activity). Regardless of the cause, the presence of hirsutism implies a net hyperandrogenic effect at the hair follicle. Evaluation requires a careful physical examination and the measurement of serum androgens (testosterone and dehydroepiandrosterone). The physical examination should include areas of male-pattern hair growth such as the upper lip, chin, neck, midline chest, and lower abdomen. If serum androgen levels are elevated—testosterone greater than 1.8 nmol per liter, dehydroepiandrosterone greater than 9.5 μmol per liter—then disorders of androgen overproduction such as polycystic ovary syndrome or late-onset congenital adrenal hyperplasia should be considered. If serum androgen levels are normal, then increased 5α-reductase activity is diagnosed by exclusion. Once a diagnosis has been made, treatment can be considered. The cornerstones of medical treatment involve inhibiting adrenal or ovarian androgen production; altering androgen binding to sex hormone-binding globulin (SHBG); or blocking androgen receptors.

Ovarian androgen production can be suppressed in several ways. The use of combination estrogen-progestin (oral contraceptive) therapy lowers free testosterone levels by suppressing ovarian production of androgens and increasing SHBG. Because hirsutism is commonly associated with menstrual irregularities, oral contraceptives can also provide menstrual cycle control. Gonadotropin-releasing hormone agonists, such as leuprolide acetate or nafarelin acetate, have been used successfully to treat hirsutism by inhibiting ovarian androgen production. Because of the effects of estrogen deprivation, however, long-term treatment with these agents is not feasible.

Selective suppression of adrenal androgen production may be induced with low dosages of dexamethasone. This is

particularly effective in women with elevated adrenal androgen levels due to late-onset congenital adrenal hyperplasia. Dexamethasone is administered at night so that the early morning peak in adrenal secretory activity is suppressed. Therapy is started with 0.125 mg daily and can be increased to 0.25 mg if suppression is not achieved within three months.

The single most effective treatment of hirsutism involves the blockade of androgen receptors. Spironolactone is an androgen-receptor blocker that also inhibits 5α-reductase activity. Therefore, spironolactone can be used to treat hirsutism regardless of the cause and is frequently used in combination with an agent that suppresses androgen production. Patients generally start therapy with 100 mg daily and may increase to as much as 200 mg daily. The effectiveness of spironolactone is first seen at three months and is maintained thereafter.

It is important to emphasize to patients that improvement is often not seen for three to six months. Once pharmacologic therapy has been initiated, adjunctive local treatments such as depilatories, waxes, and electrolysis can be undertaken to accelerate the desired cosmetic changes. Because hair follicles need only brief exposure to androgens to initiate growth, long-term compliance with therapy is essential to maintain satisfactory results.

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Who Is a Candidate for Norplant?

LEVONORGESTREL-CONTAINING soft plastic (Silastic) implants are a new form of contraception that many patients are requesting. The product consists of six flexible Silastic capsules that are inserted into the subcutaneous tissue of the medial arm. An aseptic technique is required. Expulsion is rare except in cases of infection or if the capsule is placed less than 0.5 cm from the incision. Positioning the implants in a fan shape at the same tissue depth during insertion makes removal easier. Removal of the implants takes twice as long as insertion because a layer of scar tissue that forms around each capsule must be incised.

The method is extremely effective in preventing pregnancy. In multicenter trials involving almost 2,500 women, 0.2 pregnancies per 100 women occurred in the first year. The cumulative five-year pregnancy rate was influenced by body weight. Only 0.2 pregnancies were noted among women weighing less than 50 kg (110 lb) over the five-year study period. For women weighing 50 to 69 kg (110 to 153 lb), the cumulative five-year pregnancy rate was 3.4 to 5.0. The rate was 8.5 for women weighing more than 70 kg (154 lb) and was noticeably worse beginning in the third year of use. In lighter women, the rate of pregnancy prevention is comparable to that with female sterilization.

The acceptability studies done in four different countries showed that the perceived advantages of the method were similar in all four countries: foremost was the ease of use, followed by effectiveness, long duration, reversibility, and arm placement. The most frequent misconception about the method was that it caused cancer or sterility. Most women requesting Norplant assume that it will work like the oral contraceptive pill, and careful counseling is needed to explain the method and emphasize how it will differ from past methods of contraception. In an overseas study, the one-year continuation rate in women without effective counseling was 60% compared with 88% when more rigorous preinsertion counseling was provided.

The predominant side effect of the implants is a disruption of the menstrual cycle. Because abnormal bleeding is an anticipated side effect, a biopsy is not recommended—even in women older than 35 years with irregular bleeding—provided they had regular cycles before insertion. Women with no menstrual bleeding are tested for urinary human chorionic gonadotropin at four and six weeks. If these tests are negative, the patient is reassured that it is a normal response to the method. Amenorrhea of pregnancy is consistently preceded by a pattern of regular monthly bleeding caused by ovulatory cycles.

Abnormal bleeding patterns improve with extended use. Those women who initially experience scant bleeding report more bleeding in subsequent years, and those with initially increased bleeding tend to bleed less with continued use. Despite changes in bleeding patterns, decreases in hemoglobin or ferritin concentration are extremely rare in Norplant users. Few women anticipate the extent of these menstrual changes—especially the unpredictability of individual response—and careful counseling is required both before and during the early months of use to prevent an early discontinuation of the method.

Patients with impaired glucose tolerance or hyperlipidemia should be carefully monitored in the initial use of the product. It is possible that the levonorgestrel may worsen these conditions or reduce the response to treatment. Women with impaired liver function may metabolize the levonorgestrel poorly, and the progestin may cause fluid retention. The product may alter vision or lens tolerance in contact lens users. Many women have constant premenstrual symptoms, and patients with a history of depression may find that the capsules precipitate a recurrence. In cases where there is some question about whether the method would be tolerated, women can be placed on a course of levonorgestrel-only oral contraceptives for a short trial (with condoms for added protection) before placing the implants.

The ease of use of the continuous-release capsules makes the method ideally suited for women who have used oral contraceptives without side effects but who forget to take their medication on a regular basis. It is also ideal for women with contraindications to estrogen and those who have estrogenic side effects from oral contraceptives. Careful attention to counseling before placement and patient selection will enhance satisfaction with the method.

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